Breaking Barriers

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Summary

Alzheimer's disease

Alzheimer's disease (AD) is an irreversible, progressive brain disease that slowly destroys memory and thinking skills, and eventually even the ability to carry out the simplest tasks. AD is the most common cause of dementia among older people. Dementia is the loss of cognitive functioning—thinking, remembering, and reasoning—and behavioral abilities, to such an extent that it interferes with a person's daily life and activities.

Although the causes of AD are not yet fully understood, its effect on the brain is clear. AD damages and kills brain cells (neurons). A brain affected by AD has many fewer cells and many fewer connections among surviving cells than does a healthy brain. As more and more neurons die, AD leads to significant brain shrinkage.

When doctors examine AD brain tissue under the microscope, they see three types of abnormalities that are considered hallmarks of the disease:

- **Tangles.** Brain cells depend on an internal support and transport system to carry nutrients and other essential materials throughout their long extensions. This system requires the normal structure and functioning of a protein called tau. In AD, threads of tau protein twist into abnormal tangles inside neurons, leading to failure of the transport system. This failure is strongly implicated in the decline and death of neurons.

- **Plaques.** These clumps of a protein called beta-amyloid may damage and destroy brain cells in several ways, including interfering with cell-to-cell communication. Although the ultimate cause of brain-cell death in Alzheimer's isn't known, the collection of beta-amyloid on the outside of brain cells is a prime suspect.

- **Vascular amyloid deposits.** Also known as cerebral amyloid angiopathy (CAA), is the accumulation of beta-amyloid on the wall of the blood vessels of the brain. Two types of CAA can be defined: CAA type 1 is characterized by Aβ accumulation in capillaries and is therefore often referred to as capillary CAA (capCAA). CapCAA is present in 51% of AD cases and correlates with severity of dementia; CAA type 2 is characterized by Aβ depositions in large non-capillary blood vessels.

  Amyloid deposition predisposes these blood vessels to failure, increasing the risk of a hemorrhagic stroke and compromising the functionality of the blood-brain barrier (BBB).

Amyloid accumulation

Defective vascular clearance of Aβ from the brain and/or an increased re-entry of peripheral Aβ across the blood vessels into the brain result in elevated Aβ levels in the brain parenchyma (plaques) and around cerebral blood vessels (CAA). At pathophysiological concentrations, Aβ forms neurotoxic oligomers and also self-aggregates, which leads to the development of CAA and plaques. Because of the pivotal role of Aβ removal in regulating the concentration of Aβ in the brain and therefore its accumulation, the transport of Aβ across the BBB might be a key event in the pathological cascade that leads to AD.

The blood brain barrier

The blood–brain barrier (BBB) is a separation of circulating blood from the brain that allows the brain to maintain a highly controlled microenvironment for neurotransmission to occur. The BBB is semi-permeable; that is, it allows some materials to cross, but prevents others from crossing. In most parts of the body, the smallest blood vessels, called capillaries, are lined with endothelial cells. Endothelial tissue has small spaces between each individual cell so substances can move readily between the inside and the outside of the vessel. However, in the brain, the

endothelial cells fit tightly together, due to the presence of tight junctions, and substances cannot pass out of the bloodstream.
BBB disruption is a common feature of virtually all neurodegenerative disorders and so, along with neuroinflammation, can be viewed as a key component in the process of neurodegeneration. Because in capCAA accumulation of Aβ occurs at the interface of the brain and the blood circulation, affecting those location responsible for the transport or the clearance of Aβ into the blood stream, the role of capCAA in affecting BBB function and integrity and therefore the involvement in Aβ clearance is of particular interest to understand AD pathophysiology.

Objectives

The presence of extensive capCAA distinguishes a subgroup of AD cases showing few or no parenchymal plaques, the characteristics of which are studied and described in this thesis. Identification of differentially expressed proteins in clinical cases that present capCAA pathology could reveal specific insight in the underlying molecular mechanism resulting in the disturbed clearance of Aβ across the BBB as well as specific biomarkers for capCAA.

Given the central role of the vascular and BBB compartments in the regulation of Aβ clearance the aim of the studies described in this thesis was to examine the role of Aβ transport proteins, as well as the expression of specific BBB/endothelial proteins in the AD/CAA brain and to elucidate the putative role of CAA in the evolution of AD pathology. To this end, my thesis focuses on vascular alterations presented in the capillary form of CAA and the common and not common features shared with “classical” AD, on proteins involved in Aβ transport across the BBB, including Aβ transporters and amyloid associated proteins, and a number of proteins that may play a significant role in the overall homeostasis and maintenance of the vascular endothelial and BBB compartment.

For the aim of this thesis the following main goals were formulated:
- Describe the neuropathological characteristics of capCAA, common features and differences with classic AD.
- Assess BBB changes in capCAA and underlying pathological pathways.

Chapter 2

This chapter describes the pathological characteristics of capCAA, the relationship between amyloid deposits in capCAA, CAA and plaques, and the distribution patterns of neurofibrillary changes, inflammatory markers, and ApoE around amyloid lesions.

Chapter 3

To investigate the differential expression of proteins between AD and capCAA brains a proteomics study was performed. We identified several proteins specifically upregulated in capCAA, the expression of which has been further validated with immunohistochemical techniques. We here investigated the expression and localization of laminin, clusterin, SAP and complement activation in capCAA and AD brains. Both laminin, clusterin, SAP and complement proteins colocalize with amyloid deposits in CAA and capCAA-affected tissue. Interestingly, we observed a more pronounced colocalization with vascular Aβ compared to amyloid plaques in AD brains.

Chapter 4

We investigated BBB alterations in capCAA with the emphasis on tight junction (TJ) changes and signs of neuroinflammation. We show that Aβ is toxic to brain endothelial cells via binding to RAGE and concomitant

oxidative stress, which ultimately leads to disruption of TJs and loss of BBB integrity, as shown by the leakage of fibrinogen in capCAA tissue.

Chapter 5

The expression and function of ABC transporters might be critical in the development of AD and (cap)CAA. We demonstrate that Pgp and BCRP are downregulated in capCAA, not in AD, and that Aβ and clusterin influence the expression level of P-gp. This might play a pivotal role in the development of the different amyloid deposits.

Conclusion

CapCAA is a distinct entity that defines sub-groups of both CAA and AD and whose pathogenesis is specifically associated with decreased clearance of Aβ at the BBB. CapCAA has a considerable influence on the BBB, affecting its integrity and function, and thereby affecting the homeostasis of the ageing brain.

We have demonstrated here that although capCAA and AD share some pathological hallmarks, several proteins involved in Aβ clearance are differentially deregulated. Proteins specifically up or down regulated in capCAA (and not in AD) might underscore altered pathogenic pathways explaining why Aβ accumulates around the brain vasculature instead of depositing as plaques in the brain parenchyma, as observed in AD. Furthermore, the identification of proteins that are clearly different between AD and capCAA cases could be used as biomarkers for the diagnosis of capCAA during life.